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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/436,060	11/08/99	KEALEY J	GERN-008/02U

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EXAMINER	
SHIBUYA,M	
ART UNIT	**PAPER NUMBER**
1635	4

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File Copy

Office Action Summary	Application No. 09/436,060	Applicant(s) KEALEY ET AL.
	Examiner Mark L. Shibuya	Group Art Unit 1635

☒ Responsive to communication(s) filed on *Nov 8, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-26* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *17, 22, 23, 25, and 26* is/are allowed.

☒ Claim(s) *1-16, 18-21, and 24* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Nucleotide and/or Amino Acid Sequence Disclosure

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s): The text of the specification discloses nucleotide or amino acid sequences but the this application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c). Also, a copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

Applicant must provide:

a. An initial computer readable form (CRF) copy of the "Sequence Listing".

b. An initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

c. A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

2. Applicants disclose nucleotide sequences in Table 1 of page 28 of the instant specification that must be identified by a SEQ ID number, pursuant to 37 CFR 1.821(d), which states: "Where the description or claims of a patent application discuss a sequence listing that is set forth in the 'Sequence Listing' in accordance with paragraph (c) of this section, reference must be made to

the sequence by use of the assigned identifier, in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application."

3. Applicant is required to comply with the corrections for the sequence listing as per above as part of a complete response to this official action.

Claim Rejections - 35 U.S.C. § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 15, 18, 19, 21, and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 15, 19 and 21 recite the limitation "an accessible region" in lines 2. There is uncertain antecedent bases for this limitation in the claims.

b. Claim 18 recites the language "a chemical substituent which is does not", which renders the claim vague and indefinite because of the improper grammatical usage of the verb "is". Correction is necessary.

c. The term "substantially interfere" in claim 18 is a relative term which renders the claim indefinite. The term "substantially interfere" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree of interference, and one of skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

d. Regarding claim 24, the phrase "the tetracycline-inducible CMV promoter (such as the human immediate-early CMV promoter)" renders the claim indefinite because "the tetracycline-inducible CMV promoter" suggest that there is only one such promoter, while the language "such as the human immediate-early CMV promoter" suggests that there is more than one such promoter.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of *in vitro* inhibition of human telomerase activity by contacting human telomerase with a polynucleotide comprising an antisense sequence that specifically hybridizes to a nucleotide sequence within an accessible region of the RNA component of a human telomerase, does not reasonably provide enablement for methods of *in vivo* inhibition of human telomerase activity in a living human subject, including gene therapies, and pharmaceutical compositions thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

a. Claims 1-11, drawn to methods for inhibiting human telomerase activity, pharmaceutical compositions, methods of treating a subject, polynucleotides, expression vectors, and methods of inhibiting human telomerase activity by targeting the human telomerase with a

polynucleotide comprising an antisense sequence of at least 7 nucleotides that specifically hybridizes to a nucleotide sequence within an accessible region of the RNA component of hTR, wherein the sequence within an accessible region is selected from the group consisting of nucleotides 137-196, 290-319 and 350-380 of hTR and wherein the antisense sequence does not hybridize to a sequence within a template region of the human telomerase, are not enabled over the full scope of the claims because of the unpredictability of the art of *in vivo* antisense inhibition and gene therapy, and the specification's lack of particular guidance and particular direction.

b. The specification at p. 2, lines 14-18, states that polynucleotides can inhibit telomerase activity in a cell by interfering with transcription of the RNA component, decreasing the half-life of the RNA component transcript, inhibiting assembly of the RNA component into the telomerase holoenzyme, or inhibiting the polymerase activity of the telomerase. The specification contemplates inhibitory polynucleotides useful for inhibiting telomerase activity "either in samples containing telomerase or in cells, including cultured cells or cells *in vivo*," (specification at p. 2, lines 5-8).

c. The specification at p. 10, lines 19-26, contemplates polynucleotides that "specifically hybridize" to the accessible regions of the RNA component of hTR. The specification at pp. 21-23 contemplates the prophetic use of expression vectors for gene therapy methods. The specification at p. 26, line 21 to p. 29, line 21, Example and Table 1, and particularly at p. 27, line 12-15 and Table 1, discloses an antisense oligonucleotide (ON) seven nucleotides in length (SEQ ID NO:12) that directs RNase H cleavage of hTR in partially purified nuclear or cytoplasmic

extracts. The specification contemplates the *in vivo* delivery of antisense oligonucleotides into living cells and whole animals, for the treatment of cancer, contraception or sterilization, immunosuppression, and as an antibiotic (specification at p. 24, line 16 to p. 25, line 25). The instant application contemplates the administration into animals, and indicates at p. 25, lines 32-34, that "systemic administration by injection is preferred", including " intramuscular, intravenous, intraperitoneal, and subcutaneous injection."

d. The specification at p. 26, lines 31-32; p. 28, Table 1; and Figure 1, discloses the identification of accessible regions of the RNA component of hTR that are not part of the template region, following preincubation of antisense oligonucleotides in partially purified nuclear or cytoplasmic extract, by RNase H susceptibility or oligodecoration.

e. The specification provides no particular guidance or particular direction for the inhibition of human telomerase activity *in vivo*. The specification discloses the binding of antisense oligonucleotides in cellular or nuclear extracts, but provides no particular guidance or particular direction for the delivery of antisense compounds into the target organ and target cells in the whole animal. The specification provides no particular guidance to addressing antisense compound toxicity, which can limit the administration and delivery of antisense compounds *in vivo*. The specification provides no particular guidance or particular direction for overcoming obstacles to gene therapy of problems in targeting, permanence and quantity of expression of the gene in question, immunogenicity, etc. The specification provides no particular guidance or particular direction for the expression of nucleotide sequence of a vector in sufficient quantity to

inhibit human telomerase activity in the living human being. The specification provides no meaningful nexus between RNAse H susceptibility and oligodecoration of the accessible region of the RNA component of hTR in partially purified nuclear or cytoplasmic extract by the employment of antisense oligonucleotides as short as seven nucleotides in length, and the inhibition of human telomerase in the treatment of patients and the specification provides no working examples of human telomerase inhibition *in vivo*.

f. The art teaches that antisense oligonucleotide (ON), ribozyme, trimer therapy and gene therapy of patients are unpredictable. Jen et al., Stem Cells 2000; 18:307-319, throughout the article, and particularly at p. 315, in reference to anti-mRNA strategies, states the "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive. . . . The key challenges to this field have been outlined above. It is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach." Green et al., J. A. Coll. Surg., (July 2000), vol. 191, no. 1, pages 93-105, throughout the article and at p. 103-104, point to problems of drug delivery, mRNA targeting, aptameric, nonantisense effects, potency, stability, toxicity as complex factors that must be overcome. Branch, TIBS (February 1998) 23, pp. 45-50, teaches at p. 49, teaches that the design of antisense oligonucleotides and ribozymes based upon the nucleotide sequence of the target gene is unpredictable and requires the screening of many antisense ON, because minor changes in sequences has been shown to have a major impact on inhibition of gene expression.

g. The art teaches that human gene therapy is experimental and unpredictable. Anderson, W.F., Human Gene Therapy, Nature, Vol. 392, SUPP. 30, (April 1998), at p. 25, paragraph 1, states the "[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease." Anderson at p. 30, paragraph 5, states that "[s]everal major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered. The reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how *in vivo* immune defenses can be overcome, and how to manufacture efficiently the vectors that we do make. It is not surprising that we have not yet had notable clinical success."

h. One of skill in the art would have to engage in trial and error experimentation to develop pharmaceutical compositions, antisense polynucleotides, expression vectors and methods for the inhibition of hTR activity in the living human patient. The quantity of experimentation required would include the sufficient delivery of antisense oligonucleotides to specific target hTR RNA in quantities sufficient to inhibit human telomerase activity in the living human subject; and the sustained and regulated expression of expression vectors comprising the antisense oligonucleotides and the delivery of antisense oligonucleotides to organ systems and cells in the human patient in a quantity that was sufficient to inhibit hTR expression. Therefore, undue

experimentation would be required of a person of skill in the art to make and use the claimed invention.

Claim Rejections - 35 U.S.C. § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

9. Claims 6, 12-16, 19-21 are rejected under 35 U.S.C. 102(e) as being anticipated by Villeponteau et al., U.S. Patent No. 5,583,016.

a. Claims 6, 12-16, 19-21 are drawn to antisense oligonucleotide, and pharmaceutical compositions thereof, whose sequence specifically binds or is complementary to a sequence found within an accessible region of the RNA component of the hTR in a telomerase ribonucleoprotein complex, but that does not specifically bind to a sequence within the template region of hTR, where the accessible region is located at nucleotides 137-196, wherein the polynucleotide specifically binds to hTR in the telomerase ribonucleoprotein complex and where the sequence of the polynucleotide is between 10-50 or 15-35 or at most 50 or less than about 50 nucleotides in length; and is DNA or RNA

b. Villeponteau et al., U.S. Pat. No:5,583,016 at col. 25, and SEQ ID NO:23, disclose an antisense oligonucleotide primer whose sequence specifically hybridizes or is complementary to a

sequence found within an accessible region of the RNA component of the hTR in a telomerase ribonucleoprotein complex, but that does not specifically bind to a sequence within the template region of hTR, where the accessible region is located at nucleotides 137-196, wherein the polynucleotide specifically binds to hTR in the telomerase ribonucleoprotein complex and where the sequence of the polynucleotide is between 10-50 or 15-35 or at most 50 or less than about 50 nucleotides in length; and is DNA or RNA, and wherein said antisense oligonucleotides *inherently* would specifically bind to hTR in the telomerase ribonucleoprotein complex.

Allowable Subject Matter

10. Claims 17, 22, 23, 25, and 26 are allowable. The closest prior art of record is that of Villeponteau et al., U.S. Pat. No:5,583,016, which teaches at col. 25, and SEQ ID NO:23, an oligonucleotide primer whose sequence specifically hybridizes or is complementary to a sequence found within an accessible region of the RNA component of the hTR in a telomerase ribonucleoprotein complex, but that does not specifically bind to a sequence within the template region of hTR, where the accessible region is located at nucleotides 137-196, wherein the polynucleotide specifically binds to hTR in the telomerase ribonucleoprotein complex and where the sequence of the polynucleotide is between 10-50 or 15-35 or at most 50 or less than about 50 nucleotides in length; and is DNA or RNA, and wherein said antisense oligonucleotides *inherently* would specifically bind to hTR in the telomerase ribonucleoprotein complex. However, the reference of Villeponteau et al. does not teach or fairly suggest: 1) further modifying said oligonucleotide primer to comprise non-natural nucleotide linkages or chemical substituents; 2)

the specific and exact polynucleotides of SEQ ID NOs: 2-14; and 3) expression vectors comprising said oligonucleotide primer.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mark L. Shibuya (SRC),* whose telephone number is (703) 308-9355, and/or to the patent analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.
12. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader* may be reached at (703) 308-0447.
13. Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is (703) 308-0196.

Mark L. Shibuya
Patent Examiner
Technology Center 1600
April 5, 2001

JOHN L. LeGUYADER
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